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Patent Foramen Ovale and Coronary Artery Spasm: A New Patent Foramen Ovale-Associated Condition that May Explain The Mechanism of Vasospastic Angina.

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Synopsis: Patent foramen ovale may be an underlying factor in the pathogenesis of migraine, vasospastic angina, and Takotsubo cardiomyopathy. This chapter reviews the role that PFO may play in each of these clinical entities and discusses potential interventions. It also proposes a novel clinical syndrome wherein PFO may be the unifying link between migraine, coronary vasospasm and Takotsubo cardiomyopathy in predisposed individuals.

Key words: Patent foramen ovale, vasospastic angina, angina with nonobstructive coronary arteries (ANOCA), microvascular dysfunction, migraine with aura, Takotsubo cardiomyopathy Migraine, Vasoactive Substances, and Patent Foramen Ovale

Key Points:

- Patent foramen ovale may play a key role in the pathogenesis of migraine, vasospastic angina, and Takotsubo cardiomyopathy by permitting vasoactive substances to bypass the pulmonary circulation and pass into the systemic circulation.
- PFO closure may represent an effective therapeutic option in patients with the syndrome of PFO and vasospastic angina. Moreover, given the possible link between PFO and Takotsubo cardiomyopathy, PFO closure may help prevent the development of Takotsubo cardiomyopathy in susceptible patients with evidence of PFO and prior history of Takotsubo cardiomyopathy.
- Anginal chest pain with non-obstructive coronary arteries (ANOCA) is a clinical spectrum that results in varying degrees of anginal chest pain despite the lack of obstructive coronary artery disease. ANOCA contributes significantly to healthcare utilization and results in increased morbidity and mortality to patients. Underlying mechanisms include functional endothelial dysregulation and/or coronary microvascular dysfunction.
- Invasive coronary function testing can help establish a diagnosis for patients with suspected ANOCA. Moreover, categorizing patients into phenotypic subgroups may further guide medical management of patients with ANOCA.

Clinical Care Points:

- Consider evaluating for patent foramen ovale in patients with cryptogenic stroke and elevated ROPE score.
- Consider invasive coronary functional testing with acetylcholine in patients with angina and no evidence of obstructive coronary artery disease.
- Use results of invasive coronary functional testing to guide medical management of ANOCA based on specific phenotype/likely underlying mechanism contributing to symptoms.
- In patients with ANOCA, obtain a trans-cranial Doppler study to determine if there is a right to left shunt through a PFO.

Introduction

Patent foramen ovale (PFO) has been associated with migraine, and particularly migraine with aura. PFO is thought to set the stage for migraines by permitting vasoactive substances to pass to the brain that are unfiltered by the pulmonary circulation. Several neuropeptides, including calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP), and serotonin have been implicated in the pathophysiology of migraine and are under investigation as potential therapeutic targets. For example, CGRP concentrations have been shown to be elevated in patients with chronic migraine and return to normal levels with triptan therapy[1]. Serotonin, which is a prothrombotic, vasoactive substance that is usually metabolized in the pulmonary vasculature by monoamine oxidase, may further contribute to migraine development[2]. Studies have demonstrated reduction in serotonin levels after PFO closure[3]. Moreover, embolization of small platelet aggregates into the systemic circulation has been shown to induce focal transient ischemia of the cerebral circulation, which has been associated with migraine onset.[2] Whereas these prothrombotic and vasoactive substances would otherwise be cleared by the pulmonary circulation, in the presence of a PFO they may enter the arterial system, inducing cortical spreading depression, and resulting in a migraine attack.[4,5] Several studies have supported this link between PFO and migraine, particularly in those with migraine with aura[2]. A systematic review of 12 case reports of PFO and migraine found an incidence of 46% to 88.0% in those with aura[6]. Furthermore, those with PFO have been found to be more likely to develop migraine with aura, with an odds ratio of developing migraine of 5.13[2,7]. Finally, those with larger PFO's appear to be at greater risk of developing migraine with aura, with the degree of shunting characterized by both transthoracic echocardiogram (TTE) with bubble study and transcranial Doppler (TCD)[2,8,9].

The use of anti-platelet agents, such as the P2Y12 inhibitors, may be effective in patients with drug-refractory migraine and PFO. In a study of 26 patients with migraine and PFO, the addition of clopidogrel to baseline medical therapy significantly reduced headache frequency and attack duration, with fewer visual auras and less migraine associated disability[10]. A meta-analysis of 262 patients with migraine and 539 patients who were initiated on antiplatelet therapy for primary prevention of migraine after atrial septal defect closure similarly demonstrated efficacy in reducing migraine symptoms with clopidogrel. In particular, patients with migraine who were treated with P2Y12 inhibitors had a pooled response rate of 0.64 (95% confidence interval 0.43 to 0.81, P = 0.005). P2Y12 inhibitors also reduced the frequency of new-onset migraine in those undergoing atrial septal defect (ASD) closure (odds ratio = 0.41, 95% CI: 0.22 - 0.77)[11]. P2Y12 inhibitor use has also been studied in migraine after ASD closure. The CANOA trial evaluated the use of clopidogrel in addition to aspirin for the prevention of migraine attacks following ASD closure. Patients were randomized to receive dual antiplatelet therapy (DAPT) with aspirin and clopidogrel compared to aspirin alone (with a placebo). Patients in the clopidogrel group had a reduced number of migraine days and a lower incidence of migraine attacks following ASD closure[12]. These findings suggest platelet activation and coagulation play an important role in the pathogenesis of migraine.

Several studies have evaluated percutaneous PFO closure in the management of migraine with aura. The MIST trial (2008) evaluated patients with refractory migraine with 5-23 migraine days per month and utilized the STARFlex device. The primary endpoint used was the complete resolution of migraine, with the secondary endpoint of 50% reduction of headache days. There was no difference in the primary or secondary endpoints; however, there was a high frequency of residual shunting after closure and the study population had a relatively low burden of symptoms (<5 days with migraine per month)[13]. The PRIMA trial (2014) included patients with migraine with aura with greater than 3 migraine attacks or 5 migraine days per month, but fewer than 14 headache days per month. Further, all patients enrolled had documented evidence of PFO. The primary endpoint was the reduction in migraine days from baseline to 1 year with percutaneous closure with the Amplatzer device. The study was terminated early due to slow enrollment; however, there was a trend toward fewer migraine days, with a mean reduction in migraine days of 2.9 days in the closure group compared to 1.7 days in the medical therapy group[14].

The PREMIUM trial (2017) was a double blind, sham-controlled trial that enrolled patients with 6-14 days of migraine per month, who were refractory to 3 different preventative medications. All patients were established to have a right to left shunt. The primary endpoint, arbitrarily required by the FDA, was “the responder rate” which was defined as the frequency of subjects who had a reduction in migraine attacks by 50% after percutaneous closure of PFO with the Amplatzer device. Since that trial, the FDA now accepts the number of migraine days/month as the primary endpoint for medication or device trials in migraine. In the PREMIUM trial, while there was a significant decrease in mean number of migraine days per month and in the number of patients who had complete cessation of migraine attacks (both secondary endpoints), the study did not meet its primary endpoint of responder rate[15]. Had the FDA agreed to use the number of migraine days, the endpoint of the PREMIUM trial would have been met and there would be approval today for PFO closure for migraine.

To further evaluate the efficacy and safety of percutaneous PFO closure in patients with migraine, Mojadidi et al performed a pooled analysis of the PRIMA and PREMIUM trials[16]. In this analysis, the authors evaluated patient-level data from the PRIMA and PREMIUM trials and included all primary and secondary endpoints from both trials. All the endpoints were given equal importance. The endpoints included: 1) mean reduction in monthly migraine days; 2) mean reduction in monthly migraine attacks; 3) responder rate (defined above) and 4) complete migraine cessation (100% reduction in migraine attacks during the treatment phase compared with the baseline phase). The authors also performed a subgroup analysis for patients with migraine with aura compared to those with migraine without aura, as it is postulated that patients with frequent aura may benefit more from percutaneous PFO closure. Safety outcomes, including procedural complications, were also reported for all patients who underwent percutaneous closure.

The study included data from 337 randomized patients (176 who underwent closure). The baseline characteristics did not vary significantly between the two groups, and the average number of migraine days (8.3 +/- 3.1 days vs 8.2 +/- 2.8 days; p = 0.80) and migraine attacks (4.9

+/- 1.4 days vs 4.8 +/- 1.8 days; p = 0.59) were largely similar. However, the PRIMA cohort had a higher number of patients with migraine with aura and higher Migraine Disability Assessment (MIDAS) scores. The PREMIUM cohort had higher rates of mood disorders, palpitations, steroid use, and prior head trauma. With respect to effective closure rates, 3% of PRIMA patients had significant residual right to left shunt at 12 months on TEE, and 15% of PREMIUM patients had significant residual right to left shunt at 12 months on TCD. There was no difference in the change in migraine days (average number of migraine days 10 to 12 months post-PFO closure minus average number of migraine days 2 months pre-PFO closure) between those with no residual shunt and significant residual shunt.

The study found a significant reduction in monthly migraine days at 12 months between the closure group and the control group (-3.1 days +/- 4.5 days vs -1.9 +/- 4.2 days, p = 0.02). There was also a greater reduction in the mean number of migraine attacks in the PFO closure group (-2 +/- 2.0 vs -1.4 +/- 1.9; p = 0.01) and a higher rate of complete migraine cessation compared with medical therapy (9% vs 0.7%, p < 0.001). The responder rate (defined above) did not reach statistical significance but was met in 38% of the closure group and in 29% of the control (p = 0.13).

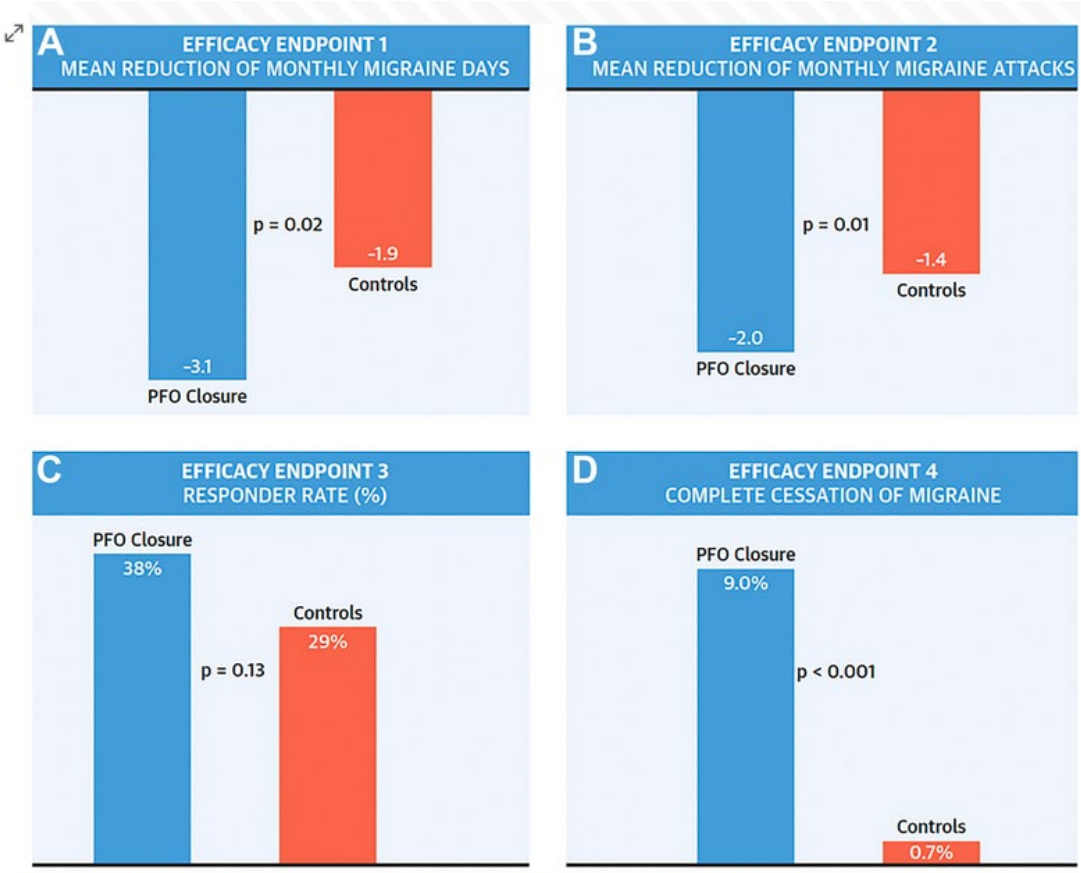
With respect to the subgroup of patients with migraine with aura, PFO closure resulted in a significant reduction in migraine days compared to the control group (-3.2 +/- 4.8 days vs -1.8 +/- 4.4 days; p = 0.03). However, those without aura did not have a significant reduction in migraine days (-2.8 +/- 3.4 days vs -2.2 +/- 4.0 days; p = 0.53). Complete headache cessation occurred in 11% of those with migraine with aura undergoing PFO closure but only in 0.9% of the control group (p= 0.002) but did not reach statistical significance in those without aura (5% vs 0%, p = 0.16). Interestingly, there was a significant reduction in the mean number of migraine attacks in those with (-2.0 +/- 2.0 vs -1.4 +/- 1.9, p = 0.09) and without aura (-2.0 +/- 1.8 vs -1.0 +/- 2.0, p = 0.03). This suggests that those without aura still may benefit from PFO closure.

Moreover, those with frequent aura (aura occurring in >50% of migraine attacks) had a greater reduction in migraine days (-4.3 +/- 5.3 days vs -1.4 +/- 4.8 days, p = 0.002), but those with infrequent aura had no significant reduction in migraine days (-2.4 +/- 3.8 days vs -2.3 +/- 3.7 day; p = 0.99). Again, complete headache cessation was significantly reduced in those with frequent aura undergoing PFO closure (13% vs 1.5%; p = 0.01) but was also significantly reduced in those with infrequent aura undergoing PFO closure (6% vs 0%, p = 0.01).

PFO closure was well tolerated with a total of 9 procedure-related adverse events and 4 device-related adverse events. The most common procedure-related adverse events included access-site hematoma and transient hypotension, and the most common device-related adverse event was paroxysmal atrial fibrillation.

This pooled analysis demonstrated a statistically significant reduction in migraine days in patients undergoing percutaneous PFO closure with the Amplatzer PFO Occluder device (Figure 1). Patients with migraine with aura had a greater reduction in migraine days and higher likelihood of reaching complete migraine cessation with PFO closure. While those without aura did not have a significant reduction in migraine days, they did have a reduction in mean number of migraines, which suggests that migraineurs without aura may still benefit from PFO closure. As the pathophysiology of migraine is complex and multifactorial, migraineurs with PFO with

aura and those without may share similar underlying factors and would still benefit from PFO closure. Further randomized controlled trials to evaluate PFO closure in various subsets of patients with migraine may help identify these underlying characteristics and identify those who would benefit from percutaneous PFO closure.



Efficacy endpoints of PFO closure for migraine from the pooled analysis of the PRIMA and PREMIUM trials (reproduced with permission from Elsevier).

Angina with Non-obstructive Coronary Arteries (ANOCA)

Anginal chest pain is often ascribed to obstructive coronary artery disease; however, in up to 40% of patients, angiography does not reveal obstructive epicardial coronary artery disease[17]. Prinzmetal angina, first described by Prinzmetal as non-exertional angina that is not explained by a mismatch in myocardial oxygen consumption and mediated by vasospasm, is the most well-known manifestation of anginal chest pain in the absence of obstructive coronary artery disease. Further studies have elucidated other underlying processes that may contribute to the presence of angina with non-obstructive coronary artery disease. Collectively, this has been referred to as ANOCA (angina with non-obstructive coronary arteries), or in the presence of documented ischemia, INOCA (ischemia with non-obstructive coronary arteries). ANOCA/INOCA are understood to beget a spectrum of clinical syndromes, ranging from non-exertional and

exertional chest pain to, in certain situations, even myocardial infarction (Myocardial Infarction with Non-Obstructive Coronary Arteries, MINOCA). Up to 5-10% of all myocardial infarctions may be attributed to MINOCA, and the 1-year all-cause mortality in MINOCA may be up to 3.5%[18]. ANOCA has been associated with significantly increased cardiovascular risk, impaired quality of life, and increased health care utilization.

Several potential mechanisms may underlie the development of ANOCA. However, these processes primarily result in functional endothelial dysregulation resulting in coronary vasospasm (epicardial or microvascular) and/or coronary microvascular dysfunction[5]. Understanding the pathophysiologic basis of ANOCA can help tailor phenotype-specific therapies for various subsets of patients.

While the pathophysiology of functional endothelial dysregulation is poorly understood, a multifactorial process involving autonomic dysregulation, endothelial dysfunction, smooth muscle hyperreactivity, preexisting atherosclerosis, and inflammation/oxidative stress has been hypothesized[19]. Endothelial nitric oxide appears to play a crucial role in preserving vascular tone. The loss of endothelial nitric oxide in the setting of oxidative stress may result in suboptimal vasodilation or even vasoconstriction in response to otherwise vasodilatory substances such as acetylcholine[20]. Furthermore, atherosclerosis and endothelial dysfunction are intrinsically linked, with atherosclerosis being shown to be closely linked with spasm in animal models[20]. This link has been demonstrated clinically as well, with one study demonstrating the presence of diffuse atherosclerosis or coronary calcification with IVUS imaging in up to 80% of patients with ANOCA[21].

Coronary microvascular dysfunction, on the other hand, refers to structural changes to the microcirculation in response to various stressors that ultimately increase the vascular tone. These changes include inward remodeling of coronary arterioles, resulting in increased wall to lumen ratio, and loss of myocardial capillary density. The increase in microvascular resistance results in decreased microcirculatory conductance and impaired oxygen delivery capacity, leading to anginal symptoms[22]. Risk factors associated with microvascular remodeling include smoking, hypertension, hyperlipidemia, diabetes, atherosclerosis, left ventricular hypertrophy, chronic inflammatory states and primary and secondary cardiomyopathies[19,20].

The diagnosis of ANOCA has historically been one of exclusion; however, developments in the measurement of coronary circulation have allowed for physiologic measurements that establish the diagnosis of coronary dysfunction. While the gold standard for physiologic measurement of coronary flow requires invasive measurements, several non-invasive methods may also provide information regarding coronary flow and the microvascular resistance. Positron emission tomography (PET) and cardiac magnetic resonance imaging (cMRI) can measure surrogates for coronary flow. PET measures the change in radiotracer activity between the resting and hyperemic states, and can infer coronary flow reserve (CFR). However, PET is not widely available due to its expense and the resources required. cMRI measures the T1 signal intensity that results from the diffusion of gadolinium from the microvasculature into the interstitial space, which is proportional to coronary perfusion and blood volume. This change in

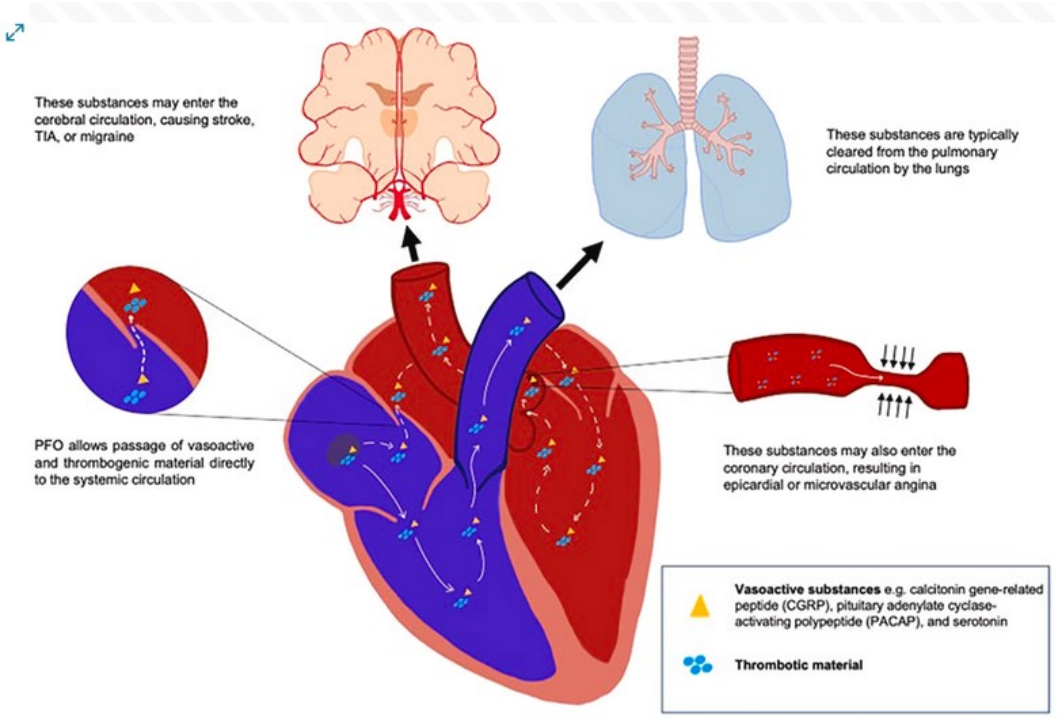
T1 signal intensity in turn can be used as a surrogate for CFR. The use of MRI derived CFR needs further validation against invasive testing. Pulsed wave transthoracic Doppler echocardiography measures coronary flow reserve at baseline and hyperemia but is only limited to assessing the left anterior descending artery, and its accuracy is highly operator dependent[18].

Invasive coronary function testing (CFT) allows for direct measurement of the various components of the coronary vasculature. CFT typically involves the evaluation of the epicardial and microvasculature for evidence of vasospasm using acetylcholine provocation testing, as well as testing of the microvasculature for the presence of coronary microvascular dysfunction (CMD) using pressure-thermistor coronary wire and coronary vasodilators[19].

Acetylcholine is typically a potent vasodilator of the coronary vasculature. However, in the presence of endothelial dysfunction, due to an imbalance in the availability of nitric oxide, acetylcholine may result in epicardial or microvascular spasm. Epicardial coronary vasospasm is diagnosed when there is a reduction in lumen size (arbitrarily defined as 90% reduction in luminal diameter) with the administration of acetylcholine, with the reproduction of anginal chest pain. Typically, testing is performed with intracoronary administration of acetylcholine in the left anterior descending artery. Further evaluation of the epicardial arteries for presence of myocardial bridging may be performed with intravascular ultrasound. Acetylcholine provocation testing is generally considered safe with a major complication rate of ~0.5%[23].

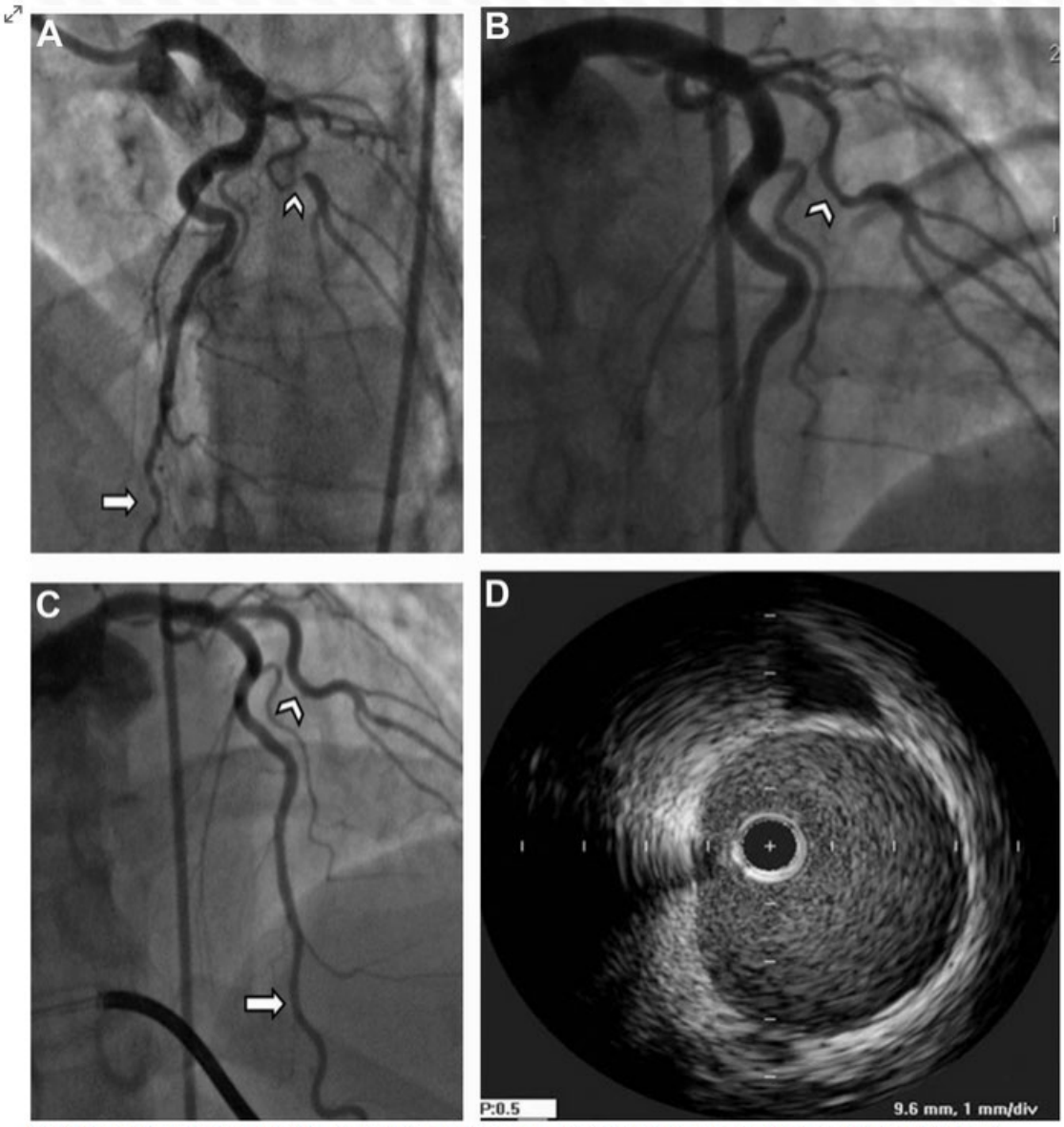
PFO and vasospastic angina

Coronary vasospasm is reversible constriction of the coronary vasculature. It is mediated by smooth muscle dysfunction, resulting in hypercontractility. Vasospastic angina occurs when there is enough narrowing of coronary arteries to compromise myocardial blood flow and cause symptoms. While the underlying mechanism mediating vasospastic angina has yet to be understood, hyperreactivity to vasoconstrictors and endothelial dysfunction are implicated[24]. PFO may play a key role in the development of angina in a subset of patients who are predisposed to smooth muscle hypercontractility. By permitting substances such as ergonovine, histamine, acetylcholine, and serotonin to pass into the coronary circulation, PFO may be a pathway that permits provocation of coronary vasospasm[25]. This proposed mechanism is depicted in further detail in **Figure 2**.



The proposed mechanism by which PFO promotes coronary vasospasm, migraine, and transient ischemic attack (TIA)/ stroke.

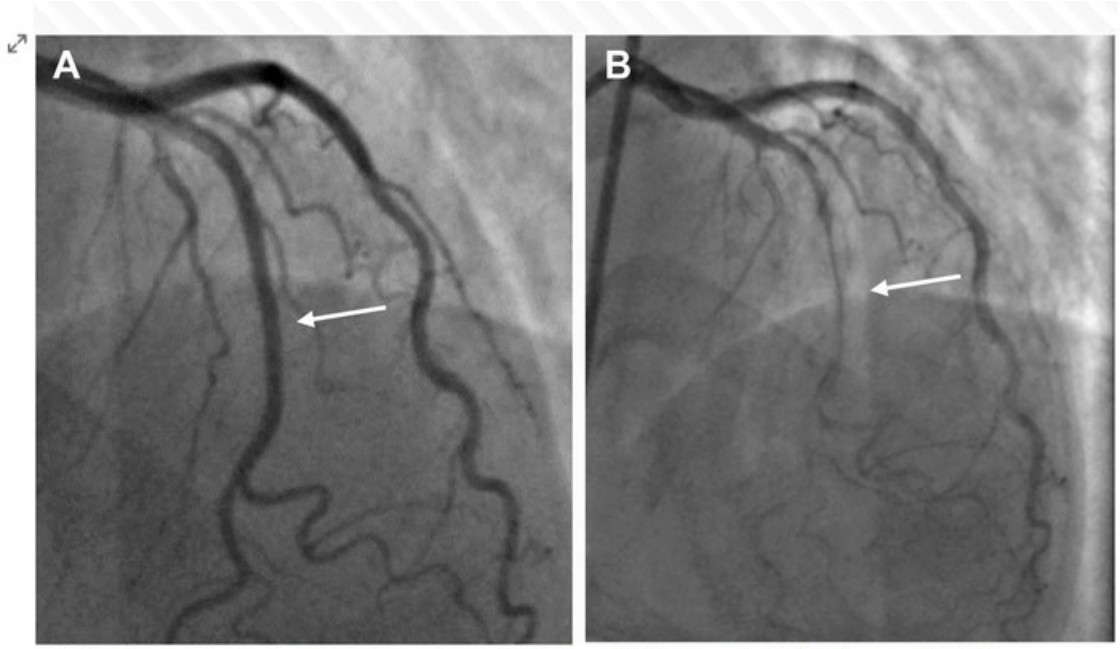
A recently published case series described 9 women with PFO who also had migraine and vasospastic angina[26]. Seven of these patients had their PFO closed (6 with percutaneous closure, 1 with surgery), and all of them had resolution in their migraine and chest pain symptoms. Interestingly, three of the patients were sisters, suggesting a strong genetic predisposition as well. The first of the three sisters had a long-standing history of migraine with aura since childhood, and a 7-year history of intermittent chest pain. At the age of 49, the patient sought treatment for severe chest pain at an emergency department when she developed ventricular fibrillation-cardiac arrest. After resuscitation, the patient underwent emergent cardiac catheterization, revealing focal narrowing of the LAD and a large diagonal vessel. The patient underwent balloon angioplasty because the physicians assumed that the coronary narrowing was due to atherosclerosis, but no stents were placed. However, no intracoronary nitroglycerin was given to rule out vasospasm. Given her migraine history she subsequently underwent transesophageal echocardiogram (TEE), which demonstrated a PFO. Repeat coronary angiography when the patient was chest pain free demonstrated normal coronary arteries with spontaneous reversal of the prior coronary narrowing, consistent with spasm. Intravascular ultrasound revealed no atherosclerosis or coronary calcification. Given resolution of the previously noted coronary artery narrowing, the patient was diagnosed with coronary vasospasm. Her PFO was closed percutaneously, and she has had no chest pain or migraines since closure (**Figure 3**).



(*A*) Angiogram demonstrated focal narrowing of the distal LAD (*arrow*) and more diffuse narrowing of the first diagonal artery (*caret*). (*B*) Angiogram after balloon angioplasty demonstrated persistent narrowing of the first diagonal artery. (*C*) Angiogram 6 months later demonstrated no evidence of coronary artery disease. (*D*) Intravascular ultrasound demonstrated no plaque in the LAD.

The patient's 68-year-old sister developed chest pain after infection with COVID19. She also had a long-standing history of migraine with aura. She underwent a thorough chest pain work up, including CT pulmonary angiogram and coronary CT angiogram, which demonstrated no pulmonary embolism or coronary artery disease. However, a small PFO was noted. Given the largely unrevealing work up and her recent COVID-19 infection, the patient was presumed to have pericarditis and was treated with a course of non-steroidal anti-inflammatory drugs. However, she developed recurrent chest discomfort and given her sister's history of chest pain associated with PFO, she underwent further work up for a shunt. A Transcranial Doppler demonstrated a Spencer grade 5/5 right to left shunt and provocative testing for coronary

vasospasm was pursued. Her baseline coronary angiogram was without any evidence of coronary artery disease; however, with administration of 100ug of acetylcholine, the patient had significant vasospasm with angiographic evidence of luminal narrowing and had reproduction of her chest pain symptoms (**Figure 4**). She subsequently underwent percutaneous PFO closure with a 25mm Gore-Cardioform occluder device. She has had no recurrent chest pain or migraine since.



(*A*) Baseline angiogram demonstrating angiographically normal LAD (*arrow*). (*B*) Angiogram after 100 µg acetylcholine I.C. demonstrating diffuse narrowing of the LAD (*arrow*).

Similarly, five other patients aged 43 to 68 years old with PFO, migraine and vasospastic angina were described who underwent PFO closure with complete resolution of symptoms. Their presenting symptoms, work up, and clinical course are described in further detail in **Table 1**. Thus, the PFO pathway may represent a novel mechanism to explain the coronary vasospasm that occurs in ANOCA. If these observations are replicated in future studies of ANOCA, PFO closure may become a powerful intervention for those with PFO-associated coronary vasospasm. We do not know the frequency of PFO in patients with ANOCA, but this could be obtained easily in those centers who see many ANOCA patients. Mechanistically, PFO closure eliminates the right to left shunting that may occur with increased intrathoracic pressure. The elimination of the right to left shunt through the PFO, forces all venous blood carrying vasoactive substances to pass through the pulmonary vasculature, where the vasoactive substances may be cleared. Further systematic investigations with randomized controlled trials are warranted.

TABLE
Table 1
Clinical features of patients with clinical syndrome of migraine, vasospastic angina, and patent foramen ovale

Case	Presentation	Migraines	Chest Pain	PFO Evaluation	Angiography	Provocative Testing	PFO Closure	Medical Therapy	Residual Symptoms/Length of Follow-up
1	49F with long-standing history of migraine with aura and intermittent angina for 7 y, who presented with chest pain and ventricular fibrillation	Yes	Yes	TEE	Index study with focal narrowing of distal LAD with repeat study demonstrating resolution of previously seen focal stenosis	No	Yes	Clopidogrel and ASA for 1 mo, ASA thereafter	No symptoms at 15 y follow-up; closed 2008
2	68F (sister of case 1) with several years of migraine with aura and recent onset angina after COVID-19 infection	Yes	Yes	TCD with 5/5 right-to-left shunt	No epicardial coronary artery disease	+Ach with narrowing of LAD (see Fig. 1)	Yes	Clopidogrel and ASA for 1 mo, ASA thereafter	No symptoms at 11 mo follow-up
3	38F with long-standing migraine history and 10 y of intermittent angina, found to have nocturnal hypoxemia to 80%	Yes	Yes	• TEE right-to-left shunting • TCD with 5/5 right-to-left shunt	No epicardial coronary artery disease	+Ach with no epicardial narrowing but with reproduction of anginal chest pain but without ECG changes	Yes	Clopidogrel and ASA for 1 mo, ASA thereafter	No symptoms at 6 mo follow-up
4	51F (sister of case 1 and 2) with migraine and history of 2v CABG for SCAD, with recurrent angina	Yes	Yes, after CABG for presumed SCAD (initial diagnosis made at OSH)	TCD with 4/5 right-to-left shunt	Mild luminal irregularities in the epicardial coronary arteries with atretic left internal mammary artery-left anterior descending artery and absent radial-left circumflex artery	+Ach with narrowing of LAD	Yes	Clopidogrel and ASA for 1 mo, none since	No symptoms at 13 y follow-up; closed 2010
5	50F with migraines with visual aura, TND (right arm numbness and weakness, with right paralysis) and several months of angina	Yes, with visual aura	Yes	TEE with right-to-left shunting	N/A	N/A	Yes	Metoprolol	• No angina at 4 y follow-up • Reduced visual auras (from 20–30 episodes/y to <6 episodes/y)
6	34F with mixed connective tissue disorder, recurrent migraines and several months of angina	Yes, with aura	Yes	• TCD with 5/5 left-to-right shunt • TEE with left-to-right shunting	No epicardial atherosclerosis, mild myocardial bridge in the distal LAD	+Ach with >90% narrowing	Deferred in favor of clopidogrel therapy, now pending PFO closure	Clopidogrel	• Angina (15 d/mo) despite clopidogrel use at 5 mo follow-up with skin bruising • Mild improvement in migraines with aura
7	43F with migraines with visual aura, TND symptoms, factor V Leiden, and recurrent episodes of angina (3–5 × per week, improved with nitroglycerin)	Yes, with visual aura	Yes, nitrate responsive	TEE with right-to-left shunt and atrial septal aneurysm	N/A	N/A	Pending	Clopidogrel Nitroglycerin spray PRN	• Improvement in angina with nitroglycerin and clopidogrel with no improvement in migraine • Has transitioned to ticagrelor with improvement in migraine
8	47F with hypertension, obesity, IDDM, OSA, migraine, hypoxemia, and recurrent angina	Yes	Yes	• TEE with right-to-left shunt • Large shunt	No epicardial coronary artery disease	+Ach with narrowing of LAD	Yes	• Clopidogrel + ASA followed by ASA monotherapy	• Occasional angina subsequently (2–3 × per month) • Improvement in migraine (now

Takotsubo Syndrome and Coronary Vasospasm

Coronary vasospasm has also been implicated in the pathogenesis of Takotsubo cardiomyopathy. Proposed mechanisms for development of Takotsubo cardiomyopathy include spasm in response to increased autonomic tone or other stimulus resulting in increased levels of catecholamines, microvascular spasm, and neuroendocrine stimulation resulting in myocardial toxicity[27,28]. That Takotsubo is associated with elevated serum catecholamine and stress neuropeptide levels is well-established. However, recent studies have implicated endothelial dysfunction resulting in coronary vasospasm as another underlying process contributing to Takotsubo. Indeed, up to 21% of patients with Takotsubo develop coronary vasospasm with provocative testing[27,29,30].

In a case series of 4 patients, Angelini et al demonstrated severe narrowing of the coronary arteries in patients with left ventricular apical ballooning with provocation testing with acetylcholine[31]. One patient was noted to have reproduction of left ventricular apical ballooning during acetylcholine administration. Similarly, in a study of 30 patients with Takotsubo, Kurisu found that provocative testing resulted in simultaneous, multivessel coronary spasm in either the epicardial or microvascular vessels[29]. These findings strongly support vasospasm as a central process in the pathophysiology of Takotsubo cardiomyopathy.

Lastly, the fact that post-menopausal women are predisposed to Takotsubo cardiomyopathy may suggest estrogen-related endothelial dysfunction[28]. Animal studies have demonstrated the benefit of estrogen supplementation, in addition to alpha and beta-adrenoreceptor blockers, in preventing Takotsubo[28,32].

Considering that endothelial dysfunction and vasospasm are key factors in the development of Takotsubo cardiomyopathy, the presence of PFO may be an underlying factor in the

pathogenesis of Takotsubo cardiomyopathy. While this hypothesis has not been fully investigated, there have been case reports suggesting a link between PFO and Takotsubo cardiomyopathy. Takafuji reported a case of a 16-year-old patient with PFO who suffered embolic stroke and was found to have reverse Takotsubo cardiomyopathy, suggesting hyperreactivity of the coronary circulation resulting in Takotsubo cardiomyopathy[33]. Further investigation is warranted to elucidate the mechanistic relationship between PFO and Takotsubo Syndrome. Evaluation for the presence of PFO may identify individuals at risk for development of Takotsubo cardiomyopathy, and patients who may benefit from prophylactic PFO closure.

In summary, patent foramen ovale may play a significant role in the development of migraine, vasospastic angina, and Takotsubo cardiomyopathy. The diagnosis and management of chest pain contributes greatly to the cost of healthcare and leads to significant morbidity. While, further research is necessary to fully elucidate the mechanistic link between PFO and these clinical symptoms, percutaneous closure of PFO has been demonstrated to reduce burden of symptoms and improve quality of life. Further characterizing the clinical syndrome of PFO, vasospastic angina, and migraine, as well as the risk factors that predispose specific individuals to these symptoms, may help identify individuals who would benefit from PFO closure. Moreover, early closure of PFO in susceptible individuals may even prevent more severe sequelae, such as Takotsubo cardiomyopathy or paradoxical embolism.

Figure legends:

Figure 1: Efficacy Endpoints of Patent Foramen Ovale Closure for Migraine from the Pooled Analysis of the PRIMA and PREMIUM Trials (reproduced with permission from Elsevier)

Figure 2: The proposed mechanism by which PFO promotes coronary vasospasm, migraine, and TIA/stroke.

Figure 3a: Angiogram demonstrated focal narrowing of the distal LAD (arrow) and more diffuse narrowing of the first diagonal artery (caret)

Figure 3b: Angiogram after balloon angioplasty demonstrated persistent narrowing of the first diagonal artery

Figure 3c: Angiogram 6 months later demonstrated no evidence of coronary artery disease

Figure 3d: Intravascular ultrasound demonstrated no plaque in the LAD

Figure 4a. Baseline angiogram demonstrating angiographically normal LAD (arrow)

Figure 4b. Angiogram after 100ug acetylcholine I.C. demonstrating diffuse narrowing of the LAD (arrow).

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